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(54) Title: COMPOSITIONS FOR TREATING HYPOXIA-ASSOCIATED OCULAR COMPLICATIONS

(57) Abstract

A method of preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises administering to the eye of the host a prophylactically or therapeutically effective amount of at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant, as well as an aqueous ophthalmic composition useful therefor.

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Compositions for treating hypoxia-associated ocular complications

This is a continuation-in-part of U.S. Patent Application Serial No. 08/079,025, filed June 18, 1993, which is incorporated herein by reference.

Field of the Invention

This invention generally relates to a method for the treatment of eye disorders. More specifically, it relates to a method and composition for preventing or treating hypoxia-associated ocular complications which employs at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant agent.

Background of the Invention

The majority of people wearing non-gas permeable hard (PMMA; polymethylmethacrylate) lenses, and a significant percentage of soft contact lens wearers experience mild to moderate corneal edema during lens wear. In "extended wear" lens users, the incidence and severity of corneal edema is greater, particularly during sleep. Other corneal complications resulting from the extended lens wear are corneal inflammation, ulcerative keratitis, infection, neovascularization, epithelial microcysts and endothelial polymegathism.

Contact lens wear causes corneal epithelial hypoxia, which results in stimulation of anaerobic glycolysis and increased production and accumulation of osmotically active lactate in the epithelium. The lactate diffuses to the stroma, where it creates an osmotic imbalance leading to increased corneal hydration (swelling). Lens wear also produces an increase in CO_2 tension brought on by limited CO_2 lens transmissibility. This increase in CO_2 at the tear-film/lens interface, combined with accumulation of stromal lactate, contributes to a

reduction in corneal pH (corneal acidosis). When the eye lids are closed, the CO_2 tension will increase further and the epithelial oxygen availability is further reduced. These effects lead to a sustained decrease in epithelial pH while a lens is being worn and the acidification will be at its greatest when the eyes are closed. This acidification could easily lead to many corneal changes, which are responsible in part for the above-indicated corneal complications.

One solution to preventing the hypoxia would be the use of contact lens material of higher oxygen permeability (e.g., a siloxane or silicon copolymer). Unfortunately, even lenses of the highest oxygen permeabilities are known to cause significant corneal edema.

Osmotic therapy using hypertonic NaCl is being practiced, but it also affects the normal cornea. Lactate dehydrogenase (LDH) inhibitors, sodium oxalate and sodium oxamate, have been reported to inhibit the progress of experimental edema by reducing the accumulation of stromal lactate without having any effect on corneal thickness in nonedematous cornea *in vitro* (M.D. Rohde et al., Current Eye Research, 1986, 5, 751-758). See also M. E. Clark, J. A. M. Hinke and M. E. Todd, J. Exp. Biol. (1981), 90, 43-63, which is incorporated in its entirety by reference.

U.S. Patent No. 5,102,670 to Abraham, incorporated herein by reference, discloses a method for treating or preventing ocular swelling and corneal-conjunctival inflammation. The method involves administration to the eye of an amount of a heme oxygenase inducing agent such as $SnCl_2$. See also Nahas, G. G., Pharmacol. Rev., 14 (1962), 447, which is incorporated herein in its entirety by reference. An increase of heme oxygenase leads to a decrease in 12(R)-hydroxy-eicosatetraenoic acid [12(R)-HETE] and 12-hydroxy-5,8,14-eicosatrienoic acid [12(R)-DIHETE] in the arachidonic acid cascade. 12(R)-HETE is known to inhibit corneal endothelial ATPase (adenosine triphosphatase) which is an enzyme responsible for maintaining proper corneal water content and thus thickness. 12(R)-DIHETE is a chemical

mediator responsible for vasodilation of conjunctival blood vessels and inflammation. Therefore, an increased level of heme oxygenase eventually leads to diminished corneal swelling and inflammation in the conjunctiva and cornea.

However, Geroski et al. Invest. Ophthal. Vis. Sci., Vol. 34, no. 4, 1404, 1993, have recently shown that 12(R)-HETE can inhibit corneal endothelial ATPase by at most 29%. This fact, together with the known osmotic effects of high corneal stromal lactate to increase corneal swelling through a purely physical-chemical mechanism, the observations of Conners et al., Invest. Ophthal. Vis. Sci., Vol 33, No. 4, 780, 1992, that heme oxygenase induction reduced contact lens induced corneal swelling by only 26%, and the reported insolubility and instability of stannous chloride in aqueous solution at physiological pH (Merck Index, 11th ed., 1989, pp. 1384-1385; Kodima et al., J. Radioanal. Nucl. Chem., Letters 146 (1) 57-66 (1990)), indicates that while some progress is being made to prevent hypoxia-associated corneal complications, there is a definite need for an improved method or ophthalmic composition to prevent or treat hypoxia complications. With the advent of extended wear contact lenses, it becomes increasingly important to avoid such problems.

Summary of the Preferred Embodiments

Surprisingly, it has been discovered that a combination of at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant agent are very effective not only for treating hypoxia-associated ocular complications, but also for preventing the same in a host in need of such treatment or prevention.

In one aspect, the present invention provides a method of preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises administering to the eye of the host a prophylactically or therapeutically effective amount of at least two agents selected from the group consisting of an

aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant.

In another aspect, the present invention provides an ophthalmic composition for preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises a prophylactically or therapeutically effective amount of at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer and an osmoprotectant, together with a physiologically acceptable carrier.

In general, the present invention involves administration to the eye of a subject an ophthalmic composition including (a) up to about 2.5% by weight of an aqueous soluble, solution-stable heme oxygenase inducer; (b) up to about 0.5M of a membrane-permeable anti-acidosis buffer; (c) up to about 0.6M of an osmoprotectant; (d) up to about 2.0% by weight per volume of a tonicity adjusting agent; and (e) water, wherein the composition has a pH range of about 6.0 to about 9.0 and wherein at least two components selected from (a), (b) and (c) are present in the composition.

Detailed Description of the Preferred Embodiments

The ophthalmic compositions of the present invention are physiologically acceptable in that they are safe and tolerable in the eye and have no significant ocular side effects.

While the composition is open to the inclusion of various other ingredients that will not detract from its efficacy, stability or physiological acceptance, preferred examples of the ingredients are provided below for purposes of illustrative clarity.

As used herein, the term "prophylactically effective amount" means that the amount of the active ingredients contained in the composition is of sufficient quantity to prevent hypoxia-associated complications by administration of the composition prior to, or simultaneously with, exposure of a host to a condition where such

complications are anticipated. For example, when contact lens wear is expected to continue for an extended period of time, prior or simultaneous administration of the composition would be required.

As used herein, the term "therapeutically effective amount" means that the amount of the active ingredients is of sufficient quantity to abrogate or ameliorate hypoxia-associated complications, including reduced wearing time, by administration of the composition before, simultaneously or after a host has developed clinical signs and symptoms resulting from such complications.

Both amounts can vary greatly according to the effectiveness of each active ingredient, the age, weight, and response of the individual host as well as the nature and severity of the host's clinical signs and symptoms. Accordingly, there is no upper or lower critical limitation upon the amount of the active ingredient. The required quantity to be employed in the present invention can readily be determined by those skilled in the art.

As used herein, the term "hypoxia-associated ocular complications" refers to any adverse conditions in which the eye or parts thereof, such as the cornea and conjunctiva, develop arising from prolonged contact lens wear which causes a state of hypoxia. Such complications include, without limitation, conditions such as corneal edema, ocular inflammation and reduced lens wearing time.

The ophthalmic composition of the present invention principally employs at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant, together with a physiologically acceptable carrier.

The aqueous soluble, solution-stable heme oxygenase inducer includes any compound or combination of compounds known to induce heme oxygenase *in vivo*. Representative compounds are aqueous soluble, solution-stable heme derivatives, heavy metal ions or suitable metal-containing compounds, and Vitamin B_{12}. Suitable heavy metal

ions are an ion of a metal selected from the group consisting of Cr, Mn, Fe, Ni, Cu, Zn, Au, Hg, Pb, Cd, Sn, Pt and Sb. The most preferred metal ion is Sn^{2+} or Sn^{4+}. Stannic chloride, being physiologically acceptable, is a particularly preferred compound. Suitable heme derivatives are various synthetic hemes wherein Fe is replaced by other metals such as Sn, Cr, Co, Zn, or Mn, and analogous compounds wherein the porphyrin ring structure is modified as protoporphyrins or mesoporphyrins. Typical synthetic hemes are cobalt protoporphyrin (CoPP), cobalt mesoporphyrin (CoMP), and heme arginate. Combinations of heme oxygenase inducers such as Vitamin B_{12}, zinc sulfate and a soluble, solution-stable Sn^{+2} or Sn^{+4} containing complex can also be used.

An effective concentration range for the heme oxygenase inducer in the composition of the invention is generally from about 0.0005 to about 1.0 w/v%, more preferably 0.001 to 0.2 w/v% and even more preferably about 0.02 w/v%.

The membrane-permeable anti-acidosis buffer may be included in the composition to correct corneal acidosis. In general, the requirements of the buffer are: (1) it must permeate through the corneal epithelium into the interior of epithelial cells and thus must be able to buffer the intracellular pH of epithelial cells; (2) it must pass through the epithelium into the stroma and buffer acellular stromal tissue; and (3) it must be acceptable from a safety and toxicology point of view. Thus, suitable buffers should be soluble in tears, physiologically acceptable, act as a proton acceptor *in vivo* and be capable of permeating through the corneal epithelial cell membranes into the intracellular medium of the epithelial cells and must also be capable of permeating through the entire corneal epithelium into the corneal stroma. The most preferred buffer is a weak base, tris(hydroxymethyl)aminomethane (TRIS) or alternatively di(hydroxymethyl)aminomethane. TRIS has been used for the treatment of acute respiratory acidosis or metabolic acidosis which

develops during cardiac operations because of its low toxicity and excellent buffering ability (G.G. Nahas, Clin. Pharmacol. and Ther., (1963), 4, 784-802). Other organic amines can be used. Sodium bicarbonate and hydroxide ion can also be used. An effective concentration range for the membrane-permeable anti-acidosis buffer is generally from about 0.05M to about 0.50M, more preferably 0.10M to 0.30M.

The osmoprotectant may be included in the composition to regulate intracellular and/or extracellular osmotic pressure. The osmoprotectant can thus correct the uneven and/or elevated hydration across the cornea (cornea swelling) caused by the lactate accumulation. The osmoprotectant may be included in the composition to regulate intracellular or extracellular osmotic pressure. In general, the requirements of the osmoprotectant are: (1) it must permeate through the corneal epithelium into the interior of epithelial cells and thus must be able to regulate the intracellular osmotic pressure of epithelial cells; (2) it must pass through the epithelium into the stroma and osmotically regulate acellular stromal tissue; and (3) it must be acceptable from a safety and toxicology point of view. Thus, suitable osmoprotectants should be soluble in tears, physiologically acceptable, and be capable of permeating through the corneal epithelial cell membranes into the intracellular medium of the epithelial cells and must also be capable of permeating through the entire corneal epithelium into the corneal stroma.

Suitable osmoprotectants which can be used include trimethylamine N-oxide (TMAO), betaine, sarcosine, glycine and glycine derivatives (e.g., dimethylglycine), N,N-bis(2-hydroxyethyl) glycine, amino acids (e.g., L-alanine, D-alanine and β-alanine), taurine, glycerol, l-aminocyclopropane-l-carboxylic acid, octopine and trehalose. The particularly preferred osmoprotectant is TMAO. An effective concentration range for the osmoprotectant is generally from about 0.05M to about 0.6M, more preferably 0.10M to 0.40M.

It should be noted that osmoprotectants such as glycine or its active derivatives (e.g., sarcosine, dimethylglycine and betaine) or other suitable osmoprotectants (e.g., TMAO) can be used alone or with other excipients to treat hypoxia in the form of a tablet to be ingested or other suitable delivery vehicle. The glycine then is believed to build up in the wearer's system to afford protection from the hypoxia induced complications of contact lens wear. It should also be noted that osmoprotectants (e.g., TMAO) can be used alone to prevent or treat hypoxia in the form of a liquid, such as eye drops, eye washes, saline solution, contact lens disinfecting solution or multipurpose solution, and that such solutions also afford protection from the hypoxia induced complications of contact lens wear.

The heme oxygenase inducer, the membrane-permeable anti-acidosis buffer, and the osmoprotectant of the present invention can be co-administered to the eye of a host in a single combined formulation such as eye drops, eye washes and contact lens multipurpose solutions. Alternatively, they can be administered concurrently as separate dosage forms. Still further, one agent can be administered before or after administration of the other agent(s) provided that the time interval between the two (or three) is not too lengthy, i.e., not more than a few hours. It is, however, for convenience to the patient and the prescribing ophthalmologist or optometrist to use the agents as a single composition or formulation. Preferably and conveniently, the combined agents are administered in combination with a physiologically acceptable carrier. The most preferred carrier is sterile purified water.

Tonicity adjusting agents are normally required in an ophthalmic composition. The function of the tonicity adjusting agents is to make the composition physiologically acceptable to ocular tissues and to increase the comfort level upon administration. Suitable such agents include alkali metal halides, phosphates, hydrogen phosphates, and borates. Preferred are sodium chloride, potassium chloride, sodium phosphate monobasic and sodium phosphate dibasic. Typically,

sodium chloride can be present in the composition in an amount of from about 0% to about 2.0% by weight per volume of the total, more preferably in amount of about 0% to about 0.4%. Thus, the composition of the present invention can be prepared by dissolving the active components directly in the aforementioned vehicle, or the composition of the present invention can be added to known ophthalmic solutions.

In another mode of administration, the active agents of the invention may be administered to the eye in the form of a time release system, such as a contact lens, bandage lens or wafer. Such wafer systems are well known to the ophthalmological art, and are used when a uniform, controlled delivery of the active agents is desired. These systems may be made of biocompatible and biodegradable materials which degrade in the eye upon contact with a body fluid (tears) or an enzyme, and are subject to the same pharmacologically acceptable requirements as are indicated for the aforementioned solutions. In yet another method of administration an osmoprotectant selected from the group consisting of glycine, L-alanine, D-alanine, β-alanine, l-aminocyclopropane-l-carboxylic acid, sarcosine, dimethylglycine, betaine, taurine, TMAO (trimethylamineoxide) and mixtures thereof can be combined with a heme oxygenase inducer such as stannous or stannic chloride and/or Vitamin B-12, and the resulting composition ingested. Of the osmoprotectants for use in this mode of administration, glycine is preferred.

Additional ingredients may be added to the composition, as long as they are physiologically acceptable and not deleterious to the eye or ocular tissue. Further, they should not adversely affect the efficacy of the above-noted active components as well as should not deteriorate the stability of the composition. Additional ingredients are, for example, stabilizers, preservatives, disinfecting agents, buffering agents (when the anti-acidosis buffer is not present in the composition) and the like. Such ingredients are known to those skilled in the

ophthalmological art. For example, suitable preservatives and disinfecting agents include polyhexamethylene biguanide, polyquad (Onamer M), and polyoxyalkylene diamine biguanides. Generally, preservatives and disinfecting agents may be used at a concentration level of about 0.5 to 100 ppm. Suitable buffers include sodium or potassium citrate, citric acid, boric acid, sodium borate, sodium bicarbonate, various mixed phosphate buffers including combinations of Na_2HPO_4, NaH_2PO_4, Na_3PO_4, K_2HPO_4, KH_2PO_4 and $KHCO_3$. Generally, buffers may be used in an amount from about 0.05% to 2.5% by weight per volume of the total and preferably 0.1% to 2.0%. Thus, the pH of the present composition is buffered to prevent irritation to the eye by adding the buffer to the composition for pH adjustment. This buffer requirement is separate and distinct from the buffering requirements to impart anti-acidosis characteristics to the composition. In other words, the compositions can be buffered with ordinary buffers to impart pH-stability and ocular-acceptability in addition to the requirement to provide a unique membrane-permeable anti-acidosis buffer.

When contemplating the use of the active components of the invention in a contact lens wetting solution, many additional ingredients can be included in the solution to wet or rewet contact lenses in the eye. These ingredients are antimicrobial or antifungal agents, surfactants, viscosity-building agents such as lecithin or hydroxy-methylcellulose, detergent cleaners, and the like. Representative compounds for each ingredient and their use levels are ascertainable to those skilled in the ophthalmic art. For example, U.S. Patent No. 4,529,535 fully teaches the state of art, the disclosure of which is herein incorporated by reference.

The active components of the invention can be provided in solid form such as tablets or powders. Effervescing agents are typically employed when the composition is provided in solid form. Examples of

suitable effervescing agents include tartaric or citric acid used in combination with a suitable alkali metal salt such as sodium carbonate.

The effectiveness of the compositions of the present invention to prevent or ameliorate hypoxia-associated ocular complications can be determined by their ability to pass two or more of the following standard biological and/or pharmacological tests, viz., (1) measuring their ability to induce heme oxygenase to a level which adequately controls inflammation and swelling; (2) measuring their ability to reduce or eliminate corneal swelling (e.g. osmotically-induced swelling); and (3) measuring their ability to shift corneal epithelial and stromal pH to a physiologically acceptable value.

While the present invention has been described with respect to preferred embodiments thereof, it will be understood that various changes and modifications will be apparent to those skilled in the art and that it is intended that the invention encompass such changes and modification as falling within the scope of the appended claims. The following non-limiting examples are provided to further illustrate the present invention.

EXAMPLE 1

The following ingredients were combined and mixed uniformly together to produce an ophthalmic composition having a pH of 7.5:

Ingredients	Amount (% by weight)
Vitamin B_{12}	0.00085
$ZnSO_4$	0.25
NaCl	0.37
TRIS	0.25
TRIS Hydrochloride salt	1.24
Polyhexamethylene biguanide (PHMB)	1 ppm
Pluronic F127	0.10
Hydroxypropylmethylcellulose	0.10
Sterile distilled water	qs ad 100 ml

EXAMPLE 2

The following ingredients were combined and mixed uniformly together to produce an ophthalmic composition having a pH of 8.3 and osmolality of 364

mosm.:

Ingredients	Amount (% by weight per volume)
TRIS	1.49
TRIS Hydrochloride salt	0.79
TMAO	1.53
PHMB	1 ppm
Sterile distilled water	qs ad 100 ml

EXAMPLE 3

The following ingredients were combined and mixed uniformly together to produce an ophthalmic composition having a pH of 8.3:

Ingredients	Amount (% by weight)
Stannic ion soluble complex*	0.02 (stannic ion w/v%)
TRIS	1.49
TRIS Hydrochloride salt	0.79
Sodium Chloride	0.34
Polyhexamethylene biguanide (PHMB)	1 ppm
Sterile distilled water	qs ad 100 ml

*any soluble, stable, non-toxic complex of stannic ion which induces heme oxygenase

EXAMPLE 4

The following ingredients were combined and mixed uniformly together to produce an ophthalmic composition having a pH of 7.4:

Ingredients	Amount (% by weight per volume)
Stannic ion soluble complex*	0.02 (stannic ion w/v%)
TMAO	3.3
Sodium phosphate (dibasic)	0.12
Sodium phosphate monobasic	0.02
PHMB	1 ppm
Sterile distilled water	qs ad 100 ml

*any soluble, stable, non-toxic complex of stannic ion which induces heme oxygenase

What is claimed is:

1. A method of preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises administering to the eye of the host a prophylactically or therapeutically effective amount of at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant.

2. The method according to claim 1, wherein the heme oxygenase inducer is an aqueous soluble, solution-stable complex of stannic or stannous ion.

3. The method according to claim 1, wherein the buffer is tris(hydroxymethyl)aminomethane.

4. The method according to claim 1, wherein the osmoprotectant is trimethylamine N-oxide.

5. The method according to claim 1, wherein the hypoxia-associated ocular complication is corneal edema.

6. The method according to claim 1, wherein the hypoxia-associated ocular complication is ocular inflammation.

7. The method according to claim 1, wherein the hypoxia-associated ocular complication is reduced lens wearing time.

8. An ophthalmic composition for preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises a prophylactically or therapeutically effective amount of at least two agents selected from the group consisting of an aqueous soluble, solution-stable heme oxygenase inducer, a membrane-permeable anti-acidosis buffer, and an osmoprotectant, together with a physiologically acceptable carrier.

9. The composition according to claim 8, wherein the heme oxygenase inducer is an aqueous soluble, solution-stable complex of stannic or stannous ion.

10. The composition according to claim 8, wherein the buffer is tris(hydroxymethyl)aminomethane.

11. The composition according to claim 8, wherein the osmoprotectant is trimethylamine N-oxide.

12. The composition according to claim 8, wherein the heme oxygenase inducer and the membrane-permeable anti-acidosis buffer are selected.

13. The composition according to claim 8, wherein the heme oxygenase inducer and the osmoprotectant are selected.

14. The composition according to claim 8, wherein the membrane-permeable anti-acidosis buffer and the osmoprotectant are selected.

15. An ophthalmic composition comprising:

(a) up to about 2.5 w/v% of an aqueous soluble, solution-stable heme oxygenase inducer,

(b) up to about 0.5M of a membrane-permeable anti-acidosis buffer,

(c) up to about 0.6M of an osmoprotectant, and

(d) up to about 2.0% by weight per volume of a tonicity adjusting agent,

wherein the composition has a pH range of from about 6.0 to about 9.0, provided that at least two components selected from (a), (b), and (c) are present in the composition.

16. A method of preventing or treating hypoxia-associated complications of contact lens wear comprising forming a composition comprising an osmoprotectant and formulating the composition in an ingestible vehicle.

17. The method of claim 16 wherein the composition comprises glycine or its active derivatives.

18. The method of claim 17 wherein the composition further comprises a heme oxygenase inducer selected from the group consisting of stannous chloride, stannic chloride, vitamin B_{12} and zinc sulfate.

19. A method of preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises administering to the eye of the host a prophylactically or therapeutically effective amount of an osmoprotectant.

20. An ophthalmic composition for preventing or treating hypoxia-associated ocular complications in a host in need of such prevention or treatment which comprises a prophylactically or therapeutically effective amount of an osmoprotectant together with a physiologically acceptable carrier.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K45/06 A61K33/24 A61K31/68 A61K31/13 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 04905 (ABRAHAM, NADER, G. ET AL.) 2 April 1992 see abstract	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1994	18. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/06824

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-7, 16-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.